

Fluorous Phase-Enhanced Fluorescent Sensitivity for Enantioselective Recognition of Lysine

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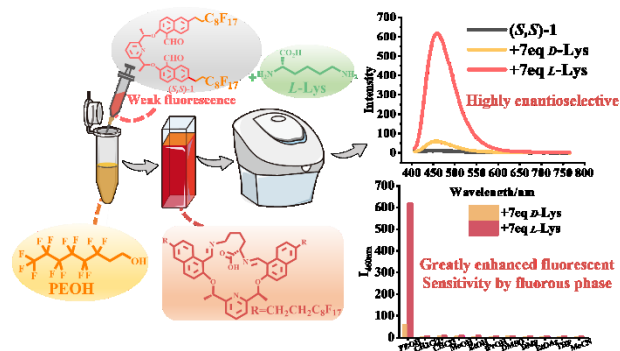
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A novel fluorinated chiral dialdehyde (*S,S*)-**1**, prepared from (*S,S*)- or (*R,R*)-2,6-bis(1-hydroxyethyl)pyridine and 2-naphthol containing a highly fluorinated alkyl group, is found to show enantioselective as well as chemoselective fluorescent recognition of lysine in the fluorous phase. It is discovered that the fluorous phase greatly enhances the fluorescent sensitivity and selectivity of the probe. Thus, the fluorous phase can not only allow the fluorescence measurement to be conducted away from common organic and aqueous media to minimize undesirable interferences, but can also provide a unique environment to greatly improve the selective fluorescent response.



Highly fluorinated materials are hydrophobic and lipophobic, but fluorophilic. These properties allow easy separation of highly fluorinated molecules from common organic and aqueous phases to the fluorous phase. In the past three decades, extensive studies have been conducted in applying the fluorous phase-based separation techniques to the development of more efficient synthesis and catalysis.¹⁻³ However, much less work has been reported for the application of the fluorous phase-based chemistry in molecular sensing.⁴⁻⁹ Previously, we reported the use of a 1,1'-binaphthyl-based perfluoroalkyl ketone for the enantioselective fluorescent recognition of chiral amino alcohols.⁶ This fluorous phase-based fluorescent sensing has been applied to screen catalysts for the asymmetric synthesis of chiral amino alcohols.⁷ Using the molecular probes to conduct fluorescent detection of reaction products in the fluorous phase can minimize the interference of other reaction components, and increase the efficiency and accuracy of the analysis.

Fluorescent detection of amino acids are useful in both biological study and chemical analysis.¹⁰ *L*-Lysine is one of essential amino acids for human body and it is involved in important processes such as proteingenesiis, fatty acid metabolism and uptake of mineral nutrients.^{11,12} *D*-Lysine is useful in medicine development¹³ and also plays role in bacterial and fungal metabolites.¹⁴ Although a number of analytic methods have been developed for the detection of lysine,^{15,16} fluorescent probes that can conduct both enantioselective as well as chemoselective recognition of lysine are rare¹⁷ and no fluorous phase-based selective lysine detection has been developed. In this paper, we report a

discovery of a fluorous phase-based enantioselective and chemoselective fluorescent detection of lysine. The fluorous phase used in this study not only can allow the detection of lysine in a phase separated from ordinary media which can avoid the interference of other substances, but has also exhibited greatly increased fluorescent sensitivity over the nonfluorinated probe used in common organic solvents.

We have designed the fluorinated chiral dialdehyde (*S,S*)-**1** for selective detection of lysine (Figure 1). The two highly fluorinated alkyl groups in (*S,S*)-**1** will enable this compound soluble in fluorinated solvents and allow fluorescence measurement to be conducted in the fluorous phase. Although various aldehydes have been actively utilized in the development of fluorescent probes for amines,¹⁸⁻²⁵ an imine product formed from the condensation of an aldehyde group with a primary amine is normally nonfluorescent due to the excited state isomerization of the imine double bond. Often, addition of a metal cation such as Zn^{2+} is needed to form chelated coordination with the imine nitrogen and restrict its excited state isomerization in order to turn on the fluorescence.²⁰⁻²⁴ Another strategy that could be used to turn on the fluorescence of an imine compound is to introduce cyclic structure to the imine product to restrict the excited state isomerization and increase the structural rigidity.²⁵ We propose that when (*S,S*)-**1** is used to interact with most amino acids, there should *not* be significant fluorescent response due to the expected formation of poorly emissive imine products from the condensation of the aldehyde groups of this probe with the amine groups of the substrates. However, when lysine is used to react with (*S,S*)-**1**, both the amine groups of lysine

could react with the two aldehyde groups of (*S,S*)-**1** to form a macrocyclic compound like **2**. The cyclic structure of **2** could restrict the excited state isomerization of the two imine bonds to generate fluorescence enhancement. Figure 1 gives a molecular modeling structure of **2** (R = H) by applying the density functional theory with Gaussian 16 software at B3LYP-D3BJ/6-31G(d,p) level. It shows that the diastereomers formed with L-Lys has a slightly lower energy than the one formed with D-Lys (see Figure S19-24 in SI).

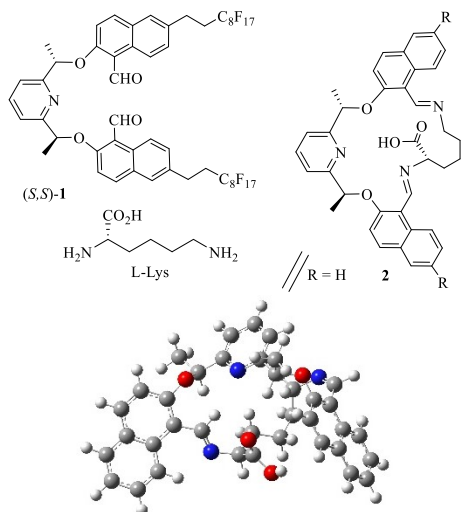
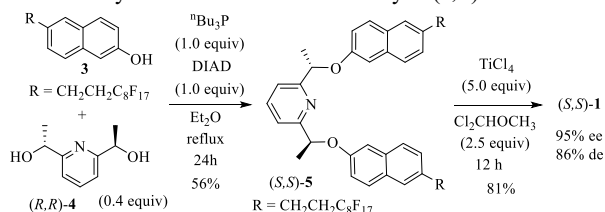


Figure 1. Design of a highly fluorinated fluorescent probe (*S,S*)-**1** for lysine and a molecular modeling structure of the cyclic di-imine product **2** (R = H).

We synthesized compound (*S,S*)-**1** according to Scheme 1. A literature Mitsunobu reaction procedure²⁶ was modified for the synthesis of compound (*S,S*)-**5** from the perfluorooctylethyl substituted 2-naphthol **3**²⁷ and (*R,R*)-2,6-bis(1-hydroxyethyl)pyridine, (*R,R*)-**4**. Treatment of (*S,S*)-**5** with TiCl₄ and methoxy dichloromethane gave the desired dialdehyde (*S,S*)-**1** in 81% yield.²⁸ HPLC-chiralcel-OD-3 column analysis shows this compound with 95% ee and 86% de (see Figure S13 in SI). In highly fluorinated solvents such as 2-(perfluorohexyl)-ethanol (PEOH) containing 1% CH₂Cl₂, it gives very weak emission at λ_{em} = 460 nm (λ_{exc} = 392 nm). Compound (*R,R*)-**1**, the enantiomer of (*S,S*)-**1**, was also prepared in the same way by starting with (*S,S*)-**4**.

Scheme 1. Synthesis of the chiral dialdehyde (*S,S*)-**1**.



We first studied the fluorescence response of (*S,S*)-**1** in the fluoruous phase (PEOH) toward lysine in water. When a solution of (*S,S*)-**1** (5.0 × 10⁻⁵ M) in PEOH/CH₂Cl₂ was

mixed with a water solution of either L- or D-Lys (7.0 equiv, HEPES buffer pH = 7.4) (PEOH:H₂O:CH₂Cl₂ = 93:6:1, v) under vortexing, however, no change in fluorescence was observed (see Figure S1 in SI). Under the same conditions, 18 common amino acids and their enantiomers also caused little fluorescence response of (*S,S*)-**1** (see Figure S2a in SI). Changing the cosolvent of PEOH from CH₂Cl₂ to THF gave similar results (see Figure S2b in SI).

Then, the fluorescence response of (*S,S*)-**1** toward the tetrabutylammonium (TBA) salts of D- and L-Lys in MeOH was investigated. When a solution of (*S,S*)-**1** (5.0 × 10⁻⁵ M) in PEOH/CH₂Cl₂ was mixed with a MeOH solution of L-Lys-TBA (7.0 equiv) (PEOH:H₂O:CH₂Cl₂ = 93:6:1, v) under vortexing, the fluorescence of (*S,S*)-**1** at λ = 460 nm was greatly enhanced (I/I₀ = 55.5) (Figure 2a). Under the same conditions, D-Lys-TBA caused much smaller fluorescence enhancement (I/I₀ = 5.3) (Figure 2a). As shown by the photos in Figure 2a, (*S,S*)-**1** can be used to discriminate L- and D-Lys visually under UV light. Effect of the concentration of lysine on the fluorescence response of (*S,S*)-**1** was studied (see Figure S3 and S4 in SI). As shown in Figure 2b, when the concentration of L-Lys-TBA increased from 0 to 7 equiv, the fluorescence enhancement reached maximum after which the fluorescence started decreasing with increasing concentration of L-Lys-TBA. The fluorescence enhancement of (*S,S*)-**1** in the presence of D-Lys-TBA was small in the entire concentration range. At 7.0 equiv L-Lys-TBA, the enantioselective fluorescence enhancement ratio [ef = (I_L-I₀)/(I_D-I₀); I_L, I_D, I₀: fluorescent intensity at 460 nm with and without L-/D-Lys-TBA, respectively] is 12.8, a highly enantioselective response.

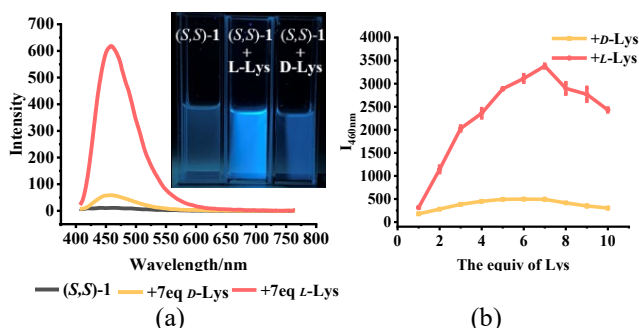


Figure 2. (a) Fluorescence spectra of (*S,S*)-**1** (5.0 × 10⁻⁵ M) with L- and D-Lys-TBA (7.0 equiv) in PEOH/MeOH/CH₂Cl₂ (93/6/1, v). Insert: Photos under 365 nm UV light. (b) Fluorescence intensity at λ = 460 nm versus the equivalent of L- and D-Lys-TBA. (Error bars from three independent experiments. λ_{exc} = 392 nm, slits = 5/5 nm, reaction time: 30 min, temperature: 25 °C).

We found that the fluorescence of (*S,S*)-**1** was greatly enhanced in 30 min in the presence of L-Lys-TBA after which only very small changes were observed (See Figure S5 in SI). D-Lys-TBA did not generate much fluorescence enhancement on (*S,S*)-**1** over 6 h. Thus, 30 min was chosen as the reaction time for all the fluorescence measurements. We also compared the fluorescence responses of (*S,S*)-**1** toward L-/D-Lys-TBA in various fluoruous solvents and found that the highest enantioselectivity was achieved in PEOH (See Figure S6 in SI). The limit of detection (LOD)

for the use of (*S,S*)-**1** to detect *L*-Lys-TBA was determined to be 2.20×10^{-7} M (see Figure S7 in SI).

We compared the fluorescence responses of (*S,S*)-**1** toward *L*- and *D*-Lys-TBA in PEOH with those in other solvents including CH_2Cl_2 , CHCl_3 , MeOH, EtOH, $i\text{PrOH}$, DMSO, DMF, EtOAc, THF and MeCN. As shown in Figure 3, almost no fluorescence enhancement was observed when (*S,S*)-**1** was treated *L*- or *D*-Lys-TBA in common organic solvents. Only in the fluorous phase, was there highly enantioselective fluorescent enhancement. This result demonstrates that the fluorous phase used in this study not only provides a different phase for fluorescence measurement, but also greatly enhances the sensitivity and enantioselectivity in the fluorescent recognition.

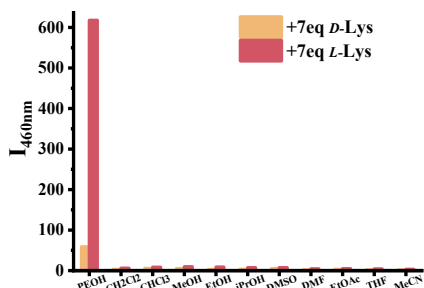


Figure 3. Fluorescence intensity at $\lambda = 460$ nm, I_{460} , for the interaction of (*S,S*)-**1** (5.0×10^{-5} M) with *L*-/*D*-Lys-TBA (7.0 equiv) in various organic solvents (0.5 mL) ($\lambda_{\text{exc}} = 392$ nm, slits = 5/5 nm. reaction time: 30 min. temperature: 25°C).

The observed large fluorescence enhancement for the chirality matched probe-substrate interaction in the fluorous phase as shown in Figure 3 could be attributed to the strong lipophobic properties of the highly fluorinated solvent. It is proposed that (*S,S*)-**1** might react with the chirality matched *L*-Lys-TBA more favorably than with *D*-Lys-TBA to form a macrocycle similar to **2**. Although the highly fluorinated R groups of **2** can make this compound soluble in the fluorous phase, the nonfluorinated macrocyclic part of this compound should not have favorable interaction with the highly fluorinated solvent. This unfavorable solute-solvent interaction should increase the structural rigidity of this macrocycle which can greatly increase its fluorescence. Whereas, in other polar organic solvents, the macrocyclic part of **2** should be well-solvated with good structural flexibility and give very small fluorescence enhancement.

We have also prepared compound (*S,S*)-**6** that contains no fluorinated alkyl substituent (Figure 4). When (*S,S*)-**6** (5.0×10^{-5} M) was treated with *L*- or *D*-Lys-TBA in MeOH/ CH_2Cl_2 (99:1, v) at 25 °C for 30 min, only a slight change in fluorescence. was observed (see Figure S8 in SI). When the reaction time was extended to 300 min, the fluorescence intensity of (*S,S*)-**6** with *L*-Lys-TBA at $\lambda_{\text{em}} = 460$ nm increased but still much weaker than that when (*S,S*)-**1** was treated with *L*-Lys-TBA in PEOH. That is, the fluorescence response of (*S,S*)-**6** toward lysine is much smaller and slower than the use of (*S,S*)-**1** in the fluorous phase as shown in Figure 4 in which the fluorescence spectrum of (*S,S*)-**6** in MeOH in the presence of *L*-Lys-TBA is compared with that of (*S,S*)-**1** in PEOH. When the

reaction temperature of (*S,S*)-**6** with *L*-Lys-TBA was increased to 35 °C, no obvious change in fluorescence response was observed in comparison with that at 25 °C (see Figure S9 in SI). The study of (*S,S*)-**6** further demonstrates that the fluorous phase is essential for the high sensitivity and enantioselectivity of the highly fluorinated probe (*S,S*)-**1** in the fluorescent recognition of lysine.

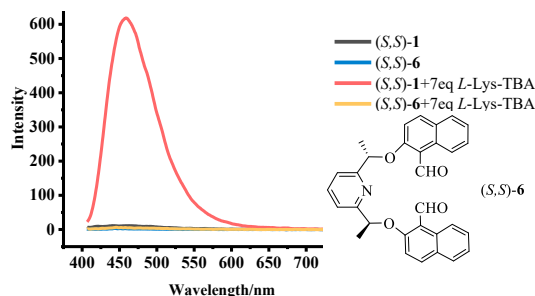


Figure 4. Fluorescence spectra of (*S,S*)-**6** (5.0×10^{-5} M) in MeOH/ CH_2Cl_2 (99:1, v) and (*S,S*)-**1** (5.0×10^{-5} M) in PEOH/MeOH/ CH_2Cl_2 (93/6/1, v) with and without *L*-/*D*-Lys-TBA (7.0 equiv). ($\lambda_{\text{exc}} = 392$ nm, slits = 5/5 nm. reaction time: 30 min. temperature: 25°C).

We used both (*S,S*)-**1** and (*R,R*)-**1** to interact with Lys-TBA at various enantiomeric excesses ($ee = [\text{L-D}]/[\text{L+D}] \times 100\%$) and the fluorescence intensities at $\lambda = 460$ nm are plotted versus ee of Lys-TBA in Figure 5. The fluorescence enhancements between (*S,S*)-**1** and (*R,R*)-**1** exhibit a mirror image relationship, which confirms the inherent chiral recognition. These probes can be used to determine the enantiomeric composition of this amino acid.

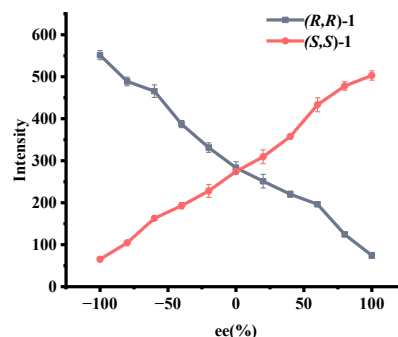


Figure 5. Fluorescence intensity of (*S,S*)- and (*R,R*)-**1** (5.0×10^{-5} M) at $\lambda_{\text{em}} = 460$ nm versus ee of Lys-TBA (6.0 equiv) (Solvent: PEOH/MeOH/ $\text{CH}_2\text{Cl}_2 = 93/6/1$, v. $\lambda_{\text{exc}} = 392$ nm, slits=5/5 nm. reaction time: 30 min. temperature: 25 °C).

We studied the fluorescence response of (*S,S*)-**1** toward 18 additional enantiomeric pairs of common amino acid-TBA salts by applying the conditions used in Figure 2. As the results in Figure S10 in SI show, no significant fluorescence enhancement of (*S,S*)-**1** was observed in the presence of most of the substrates except when phenyl alanine, isoleucine and valine were used whose fluorescence enhancements were still much smaller than the use of *L*-Lys-TBA. That is, (*S,S*)-**1** is not only a highly enantioselective

fluorescent probe for lysine but also a chemoselective one. Our NMR and mass spectroscopic analyses support the formation of a macrocyclic compound similar to **2** when (*S,S*)-**1** was treated with 1.0 equiv L-Lys-TBA (see Section 3 in SI).

In conclusion, we have designed and synthesized a novel highly fluorinated dialdehyde (*S,S*)-**1** that can carry out enantioselective as well as chemoselective fluorescent recognition of lysine in the fluorous phase. We have discovered that the fluorous solvent has greatly increased the fluorescent sensitivity of the probe. Thus, the fluorous phase can not only provide a phase to allow the fluorescence measurement to be conducted separated from the common organic and aqueous phases to minimize the potential interference of other materials, but can also provide a unique environment to enhance the sensitivity and selectivity of the probe. It is proposed that the lipophobic property of the fluorous phase could increase the rigidity of the chirality-matched sensor-substrate adduct to generate greatly enhanced fluorescence. This finding should contribute to further advancing the development of fluorescent recognition in the fluorous phase.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supplementary Information Available

Experimental procedures, additional spectroscopic data and molecular modeling study are provided.

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Notes

The authors declare no competing financial interest.

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